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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,285	06/08/2000	Guo-Liang Yu	PF343P3C4	1326

22195 7590 10/22/2003

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	17

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,285	YU ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continuation of Disposition of Claims: Claims pending in the application are 89-95,98-104,107-110,113-116,119,121,126-130,133,135,140-144,147,149,212-218,221-227,230-233 and 275-280.

Continuation of Disposition of Claims: Claims rejected are 89-95,98-104,107-110,113-116,119,121,126-130,133,135,140-144,147,149,212-218,221-227,230-233 and 275-280.

DETAILED ACTION

The finality of the rejection of the last Office action (Paper No. 13, 06 September 2002) is withdrawn in view of Applicant's persuasive arguments in Paper No. 16 (05 March 2003) and the new total lack of enablement rejection under 35 U.S.C. § 112, first paragraph, as set forth below.

Status of Application, Amendments and/or Claims

The amendment of 05 March 2003 (Paper No. 16) has been entered in full. Claims 110, 212, 221, and 230 are amended. Claims 236-242, 245-256, 259-267, and 270-274 are cancelled. Claims 279-280 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 89-95, 98-104, 107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 230-233, and 275-280 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The rejection to claims 89-95, 98-104, 110, 113-117, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 236-242, 245-249, 250-263, 275-278 under 35 U.S.C. § 112, first paragraph (scope of enablement), as set forth at pg 2-7 of the previous Office Action (Paper No. 12, 22 May 2001) are *withdrawn in part* in view of the cancelled claims and Applicant's persuasive arguments (Paper No. 13, 06 September 2002). Please see section on 35 U.S.C. § 112, first paragraph below.

2. The rejection to claims 89-95, 98-104, 107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 236-242, 245-256, 259-267, and 270-278 278 under 35

U.S.C. § 112, first paragraph (written description), as set forth at pg 7-9 of the previous Office Action (Paper No. 12, 22 May 2001) are *withdrawn in part* in view of the cancelled claims and Applicant's persuasive arguments (Paper No. 13, 06 September 2002). Please see section on 35 U.S.C. § 112, first paragraph below.

Specification

3. The disclosure is objected to because of the following informalities:

4. The Brief Description of Drawings for Figures 4A-4C at pg 20 of the specification do not make reference to the SEQ ID NO of "HNEDU15".

5. The Brief Description of Drawings for Figure 2 at pg 19 of the specification refers to Figures 2C-2D. However, there are no Figures labeled 2C-2D.

6. The Brief Description of Drawings for Figure 8 at pg 22 of the specification refers to Figure 8C. However, there is no Figure labeled "8c".

7. The Brief Description of Drawings for Figure 10 at pg 23 of the specification refers to Figures 10C-10G. However, there are no Figures labeled 10C-10G.

8. The Brief Description of Drawings for Figure 11 at pg 23 of the specification refers to Figures 11D-11F. However, there are no Figures labeled 11D-11F.

9. Patent applications are referenced throughout the disclosure (for example pg 332, [0895]). The status of the applications must be updated.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. Claims 89-95, 98-104, 107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 230-233, and 275-280 are rejected under 35 U.S.C. 112, first paragraph,

because the specification, while being enabling for **(I)** a method of stimulating B lymphocyte proliferation, differentiation, and survival comprising administering to an individual, a therapeutically effective amount of a protein comprising amino acids 134-285 of SEQ ID NO: 2, wherein said protein enhances B lymphocyte proliferation, differentiation, or survival, does not reasonably provide enablement for a method of stimulating lymphocyte proliferation, differentiation, or survival comprising administering to an individual, a therapeutically effective amount of a protein comprising all protein derivatives and fragments of SEQ ID NO: 2 recited in the claims, wherein the polypeptide modulates lymphocyte proliferation, differentiation, or survival. The specification is also enabling for **(II)** a method of stimulating B lymphocyte proliferation, differentiation, and survival comprising administering to an individual, a therapeutically effective amount of a protein comprising an amino acid fragment less than 134-285 of SEQ ID NO: 2, wherein said protein fragment can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO: 2. The specification is enabling for **(III)** a method of stimulating T lymphocyte proliferation and differentiation comprising administering to an individual, a therapeutically effective amount of (a) a protein comprising amino acids 134-285 of SEQ ID NO: 2, wherein said protein enhances T lymphocyte proliferation or differentiation or (b) a protein comprising an amino acid fragment less than 134-285 of SEQ ID NO: 2, wherein said protein fragment can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO: 2.

Additionally, the specification while being enabling for **(IV)** a method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising amino acids 134-285 of SEQ ID NO: 2, wherein said protein enhances B

lymphocyte proliferation, differentiation, or survival, does not reasonably provide enablement for a method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising all protein derivatives and fragments of SEQ ID NO: 2 recited in the claims, wherein the polypeptide modulates lymphocyte proliferation, differentiation, or survival. The specification is also enabling for **(V)** a method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising an amino acid fragment less than 134-285 of SEQ ID NO: 2, wherein said protein fragment can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO: 2.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 2-7 of the previous Office Action (Paper No. 13, 06 September 2002).

The claims are directed to a method of treating an immunodeficiency comprising administering to an individual a therapeutically effective amount of the various fragments of the amino acid sequence of SEQ ID NO: 2. The claims recite a method of treating an immunodeficiency comprising administering to an individual a therapeutically effective amount of a protein comprising the amino acid residues 134-185 of SEQ ID NO: 2. The claims recite a method of stimulating leukocyte proliferation, differentiation, or survival comprising administering to an individual a therapeutically effective amount of various fragments of the amino acid sequence of SEQ ID NO: 2. The claims recite that the immunodeficiency is common variable immunodeficiency (CVID) or Selective IgA deficiency.

Applicant's arguments (Paper No. 16, 05 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant argues that working examples are not required to satisfy the enablement criteria of 35 U.S.C. § 112, first paragraph. Applicant contends that the specification discloses that neutrokine-α promotes lymphocyte proliferation, differentiation, and survival [0153], [0154], [0156]) and Examples 6 and 7 ([0850], [0851]). It is noted that Applicant cites MacKay et al., Parry et al., Do et al., and Huard et al. as post-filing date evidence.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the Examiner acknowledges that the specification and post-filing date references indicate that neutrokine-α stimulates B cell proliferation, differentiation, and survival and activates T cell proliferation and differentiation *in vivo*. However, there is no evidence in the specification or in the post-filing date references to indicate that neutrokine-α stimulates T lymphocyte survival. Huard et al. (J Immunol 167: 6225-6231, 2001) state that an increase in T cell survival upon activation was not detected in the presence of neutrokine-α (BAFF) signaling *in vitro* (pg 6230, last paragraph). Therefore, the current state of the art is such that it does not support the claim limitation that neutrokine-α stimulates T cell (lymphocyte) survival.

(ii) Applicant asserts that all the polypeptides recited in the claimed methods are fully enabled. Applicant contends that the law does not require that Applicant forecasts the results of an experiment before it is done. Applicant submits that since the disclosed or otherwise known methods of making and screening polypeptides (and fragments or variants thereof) may be used to make and then determine, without undue experimentation, whether a given polypeptide

encompassed by the claims is able to modulate lymphocyte proliferation, differentiation, or survival and therefore possesses the disclosed utility, the enablement requirement is fully satisfied. Applicant also argues that it is not so unpredictable that one skilled in the art would be able to achieve success, i.e., be able to routinely identify polypeptide fragments and variants of SEQ ID NO: 2 that are capable of modulating lymphocyte proliferation, differentiation, or survival.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification does not teach any functional or structural characteristics of fragments, derivatives, or variants of the neutrokine-alpha polypeptide of SEQ ID NO: 2, other than polypeptides comprising amino acids 73-285 or amino acids 134-285 of SEQ ID NO: 2. The specification does not teach any methods or working examples that indicate polypeptide variants that do not contain amino acids 134-285 of SEQ ID NO: 2 have any function. For example, the specification does not teach that a protein comprising amino acid residues 271-278 of SEQ ID NO: 2 has any function. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative

substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Furthermore, the specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Undue experimentation would be required by the skilled artisan to generate the infinite number of neutrokine-α variants recited in the claims and to screen the same for activity. Therefore, based on the discussions above

concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the neutrokine-α polynucleotide sequence of SEQ ID NO: 1 to make biologically active neutrokine-α without resorting to undue experimentation to determine what the specific biological activities of the neutrokine-α polypeptide and all neutrokine-α variants are.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims that do not *entirely* contain amino acid residues 134-285 of SEQ ID NO: 2 and possibly screen same for activity and to stimulate T cell survival, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the part which establishes the unpredictability of the effects of mutation on protein structure and function and the unpredictability of stimulating T cell survival, and the breadth of the claims which fail to recite specific structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

11. Claims 89-95, 98-104, 107-110, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, and 275-280 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The basis for this rejection is set forth at pg 7-9 of the previous Office Action (Paper No. 13, 06 September 2002).

The claims are directed to a method of treating an immunodeficiency comprising administering to an individual a therapeutically effective amount of the various fragments of the amino acid sequence of SEQ ID NO: 2. The claims recite a method of treating an immunodeficiency comprising administering to an individual a therapeutically effective amount of a protein comprising the amino acid residues 134-185 of SEQ ID NO: 2. The claims recite a method of stimulating leukocyte proliferation, differentiation, or survival comprising administering to an individual a therapeutically effective amount of various fragments of the amino acid sequence of SEQ ID NO: 2. The claims recite that the immunodeficiency is common variable immunodeficiency (CVID) or Selective IgA deficiency.

Applicant's arguments (Paper No. 16, 05 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that one of skill in the art is capable of making fragments or variants of neutrokine-α that modulate lymphocyte proliferation, differentiation, or survival without undue experimentation. Applicant states that the law does not require a full disclosure. Applicant also contends that Example 14 of the Synopsis of Written Description Guidelines closely parallels the current application.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application teaches that neutrokine-alpha (SEQ ID NO: 2) is a 285 amino acid protein (pg 316, [0842]). The specification also discloses that expression of neutrokine-alpha cDNA in mammalian cells and insect cells identify a 152 amino acid soluble

form with an N-terminal sequence beginning with the alanine residue at amino acid 134 (pg 317, [0842]). However, the specification does not teach any polypeptide variants or their structural or functional characteristics wherein the polypeptide variants exclude any amino acid residues of the soluble protein (amino acids 134-285 of SEQ ID NO: 2). The description of one neutrokine-alpha polypeptide species (SEQ ID NO: 2), particularly amino acids 134-285 of SEQ ID NO: 2, is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and fragments of the neutrokine-alpha protein of SEQ ID NO: 2.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The protein itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to

lack of written description for that broad class. The specification provided only the bovine sequence.

Furthermore, the broad brush discussion of making or screening for allelic variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Also, the fact pattern in the instant application is not analogous to Example 14 in the Revised Interim Written Description Guidelines. In Example 14 of the Guidelines, the protein and variants have a specific activity disclosed in the specification. However, regarding the neutrokine-α polynucleotides and polypeptides of the instant invention, the specification does not teach any significance or functional characteristics of all possible neutrokine-α polypeptide derivatives and fragments of SEQ ID NO: 2.

Therefore, only an isolated protein comprising at least an amino acid sequence that consists of amino acids 134-285 of SEQ ID NO: 2, wherein said protein induces B cell proliferation, differentiation, and survival, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 89-95, 98-104, 107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 230-233, and 275-280 are rejected under 35 U.S.C. 112, second

paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. The term "modulates" in claims 89-95, 98-104, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, and 275-280 is a relative term which renders the claim indefinite. The term "modulates" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot be determined if "modulates" means, for example, "increases" or "decreases".

15. Claims 89-95, 98-104, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, and 275-280 recite the limitation "polypeptide" in all independent claims. There is insufficient antecedent basis for this limitation in the claims.

Conclusion

No claims are allowable

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Hammarstrom et al. Clin Exp Immunol 120 : 225-231, 2000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
15 October 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER